Implementing Quality Systems

CGMP By The Sea
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Presentation Overview

- Driving Forces - Industry & FDA
- Integration of Quality By Design, Risk Management & Quality Systems
- Modern Quality Systems
  - FDA QS Guidance
  - ICH Q10
- Implementation Issues
- Elements of Effective Quality Systems
- Quality Systems at FDA

•Implementation is evolving and aspects remain to be determined.

FDA's Path

CGMP Initiative* → Implementation

Desired State - Manufacturing

Quality By Design
Continuous Improvement/ Innovation
Process Analytical Technologies
Risk Management
Quality Systems

Desired State – Regulatory

Integrated systems
Efficient Use of Resources
International Cooperation

* Best practices approach - Internal and external
FDA Centers with varying degrees of practice

Driving Forces
(Concerns With Status Quo)

- Manufacturers quality approach
  - Is not always effective in maintaining quality environment
  - Industry should take greater responsibility for quality
- Regulatory systems and/or manufacturer's quality approach do not encourage or facilitate continual improvement, manufacturing changes and technological innovation
- CGMPs do not incorporate explicitly all concepts found in a modern quality system - interpretation
  - No requirement for a Quality System – Quality Unit functions are required
  - Continual improvement of the quality system ?
  - Continual improvement of process and product improvement ?
  - Limited proactive approach (especially with preventive actions)

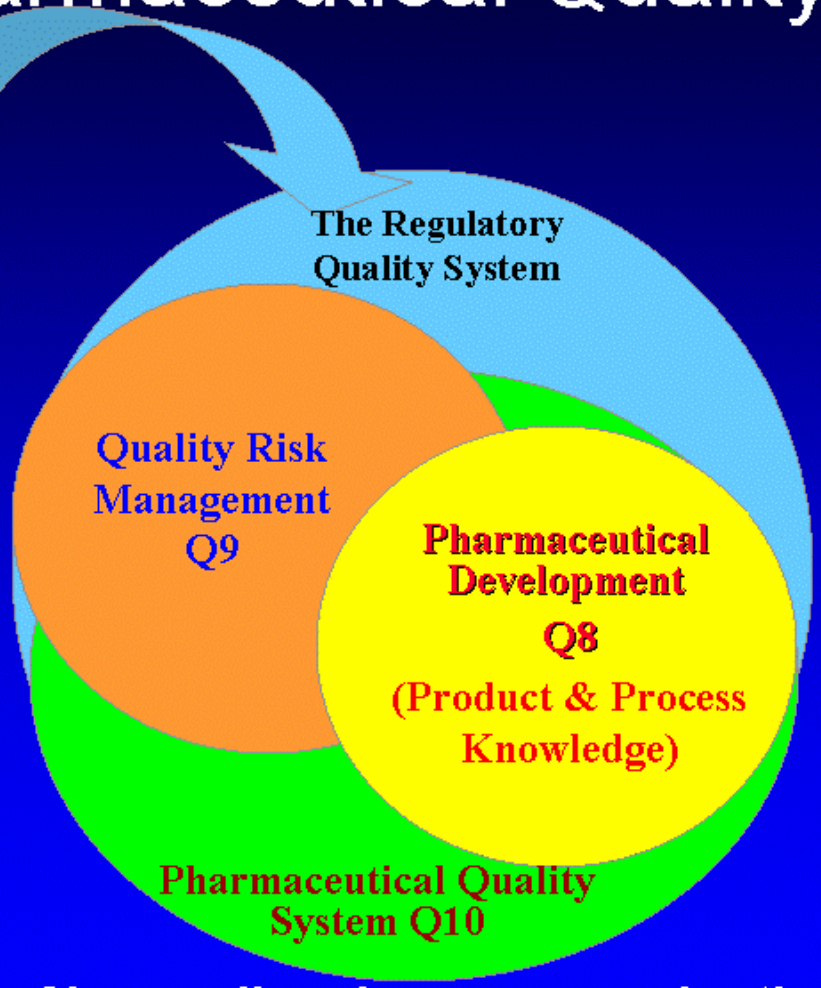
Driving Forces
(Concerns With Status Quo)

- Difficult to implement some newer regulatory paradigms (ICH Vision)
- For manufacturers, a more integrated approach to Quality Management, consistent with modern quality approaches, is needed to be able to improve product quality and implement new regulatory paradigms.

The Proposed Pharmaceutical Quality System

ICH / non-ICH topics

Includes Submission, review and inspection



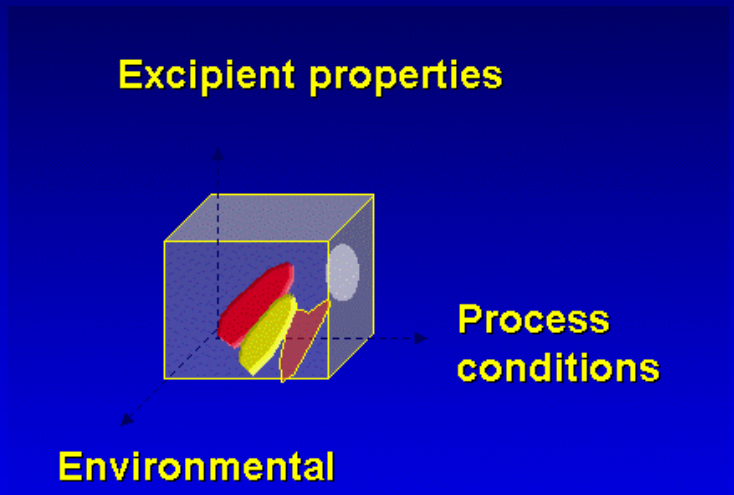
"It is not a question of how well each process works, the questions is how well they all work together." Lloyd Dobens and Clare Crawford, *Thinking About Quality*

Quality By Design

(Pharmaceutical Development Q8)

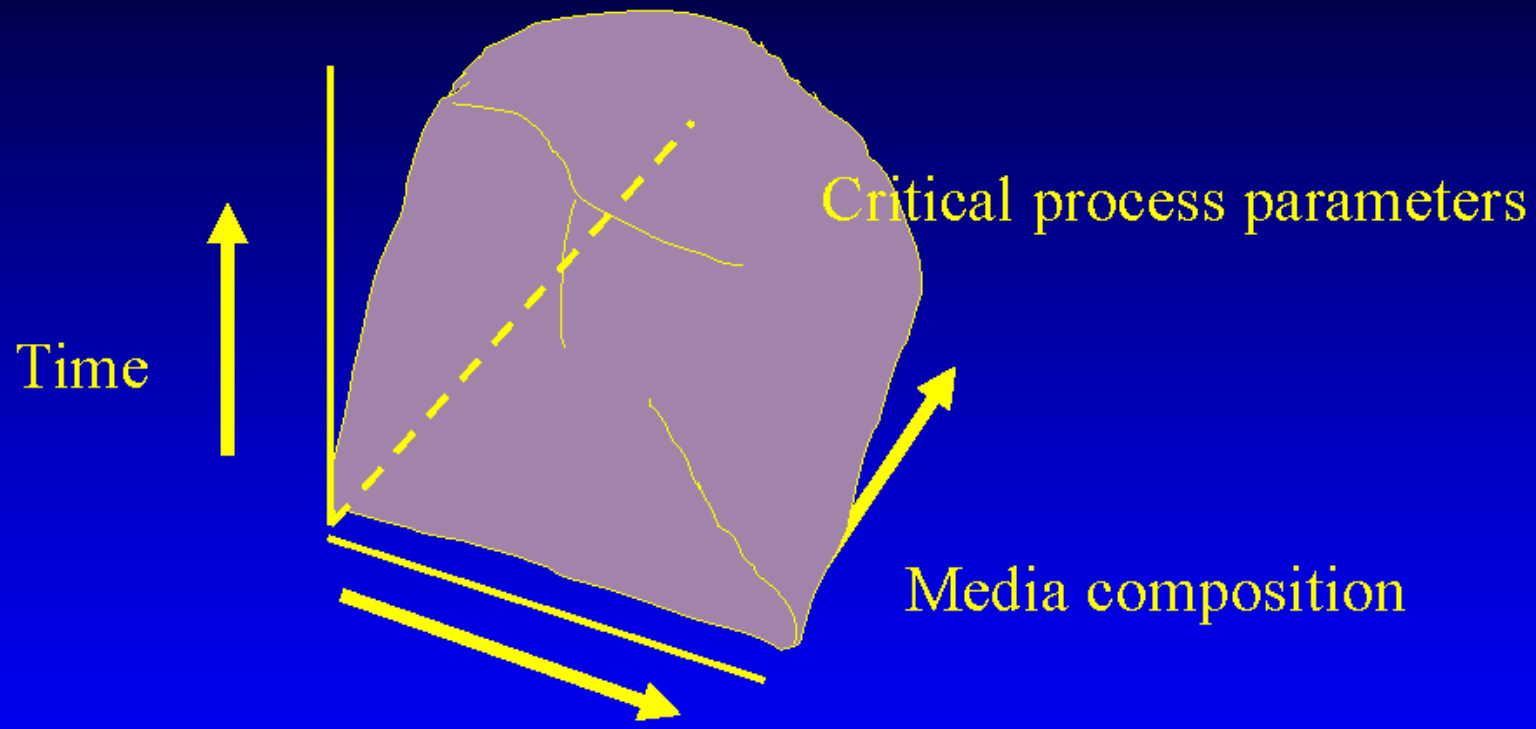
- “Quality can not be tested into products; it has to be built in by design”
- Product quality and performance **achieved and assured by design** of effective and efficient manufacturing processes
- Product **specifications based on mechanistic understanding** of how formulation and process factors impact product performance
- In doing so, can provides a framework for continuous "real time" assurance of quality and Continuous Improvement

Design Space



- Establish a Design Space
  - Multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide an assurance of quality
  - Operating within will produce a product meeting designed quality attributes
  - Working within the design space is not considered a change
  - Movement outside of design space is considered a change – subject to regulatory approval

Design Space (Fermentation)



Equipment ?
Control Space vs. Design Space ?

Quality Risk Management (Q9)

- Risk management is a key tool of a modern quality system
- Appropriate use of risk assessments throughout lifecycle
- Risk assessment is reiterative
- Decisions are based upon process and product understanding
- Relative to intended use, patient safety and availability
- Effective communication of information
  - Internal & External

Quality Risk Management (Q9)

- Identify potential hazards to process and product
- Identify potential hazards both prospectively and in a reactive mode
- Influences from all aspects of the manufacturing process for drug substance and drug product
  - Components, recipients, container closure, raw materials, dosing devices, manufacturing process, drug substance, intermediates
- How these factors influence variability of process, product performance, product safety and efficacy?

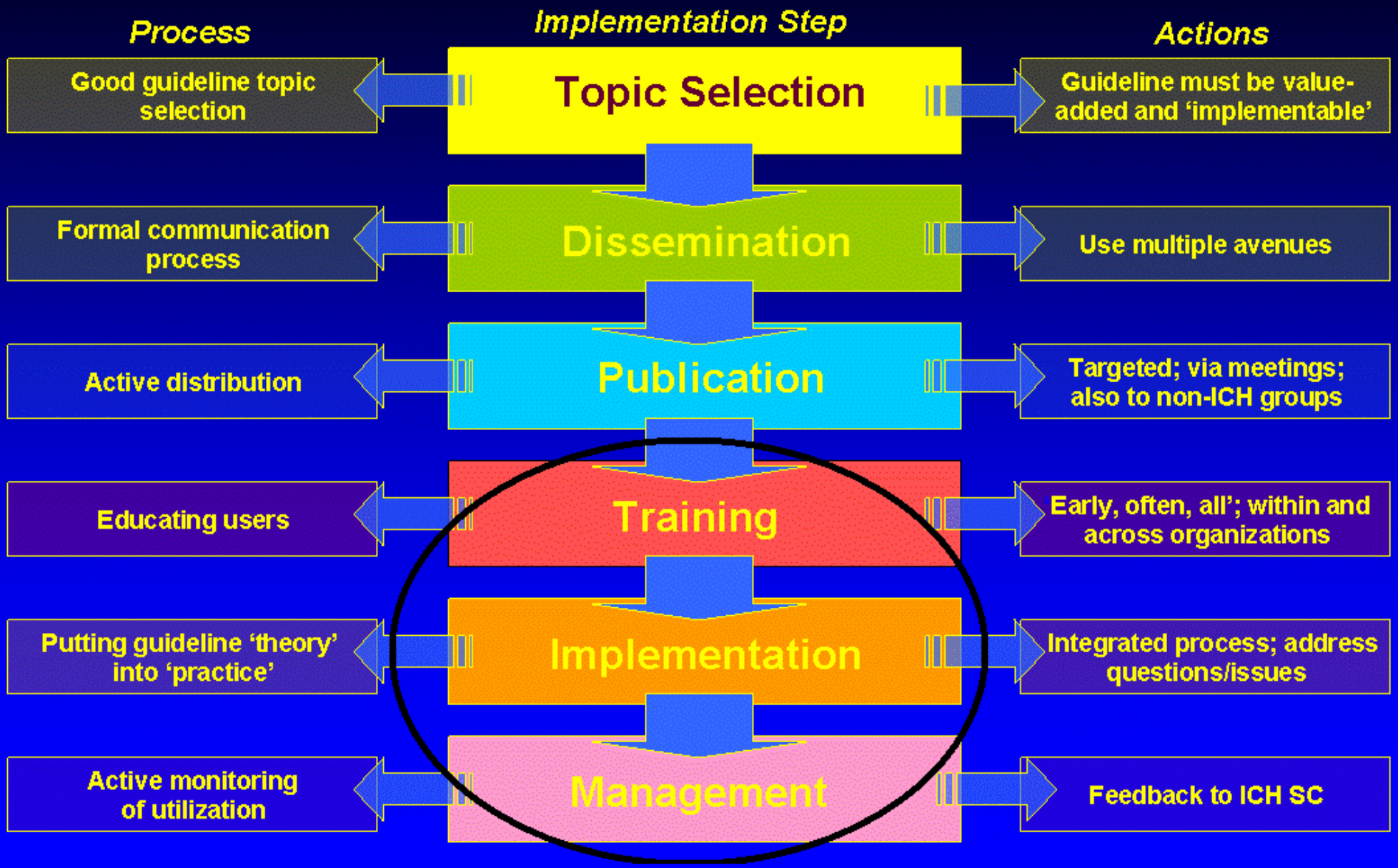
Why A Comprehensive, Modern and Robust Quality System?

- **Necessary for implementation & effective utilization:**
  - Establish a state of control, based upon modern Quality System principles, to ensure the consistent production of high quality, safe and efficacious product
  - Facilitate continuous improvement
  - Facilitate Quality By Design (Q8 Pharmaceutical Development)
    - Ability to manage movement within the design space
    - Redefine design space based upon new information
  - Facilitate Risk Management (Q9 Quality Risk Management)
  - Effective knowledge transfer & use of science and risk management
    - Review and Inspection
    - CAPA
    - Change control

Change Control

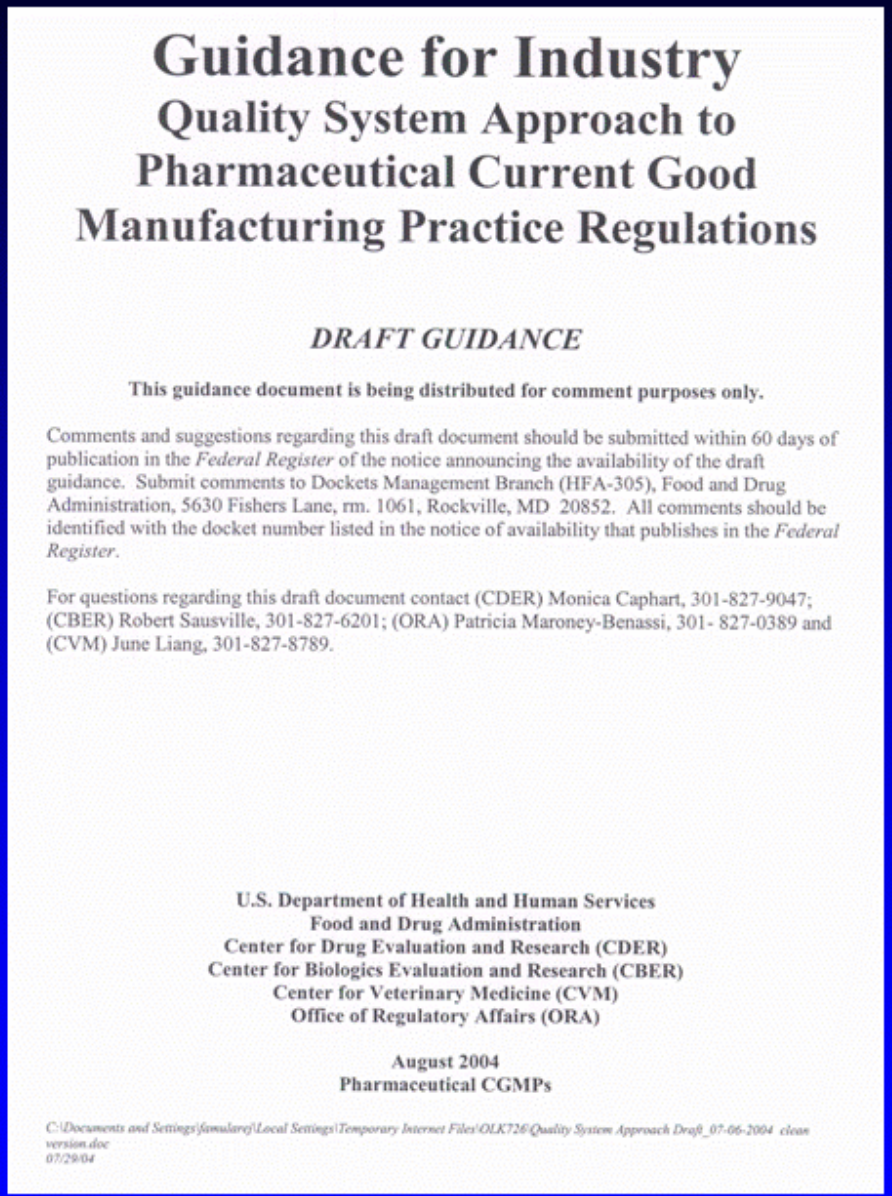
- Assure development knowledge and risk information is transferred and used appropriately
- Utilize development knowledge and risk assessment/ reduction to determine potential impact of process changes
- Assure appropriate CQA and variables are assessed
- Validation studies developed (modern concept of validation)
- Based upon product knowledge and risk assessment / reduction – assure appropriate controls are carried forward
- Ideally, correctly predict impact of change and maintain (improve) product quality

Process Flow



FDA Implementation

- Meaningful guidance
  - Consistent with and supportive of FDA goals and implementation of CGMP initiative
  - Consistent with regulations [21CFR 210 & 211] and any revisions



Guidance for Industry

Quality System Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Monica Caphart, 301-827-9047; (CBER) Robert Sausville, 301-827-6201; (ORA) Patricia Maroney-Benassi, 301- 827-0389 and (CVM) June Liang, 301-827-8789.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2004
Pharmaceutical CGMPs

C:\Documents and Settings\famularej\Local Settings\Temporary Internet Files\OLK726\Quality System Approach Draft_07-06-2004 clean version.doc
07/29/04

- Describes a modern quality systems model and relationship of CGMPs to model
- "educational guidance documents to encourage use of quality management systems principles by the regulated industry"

QS Guidance Document as a Bridge

CGMP Regulations c. 1978

21st Century Quality Systems

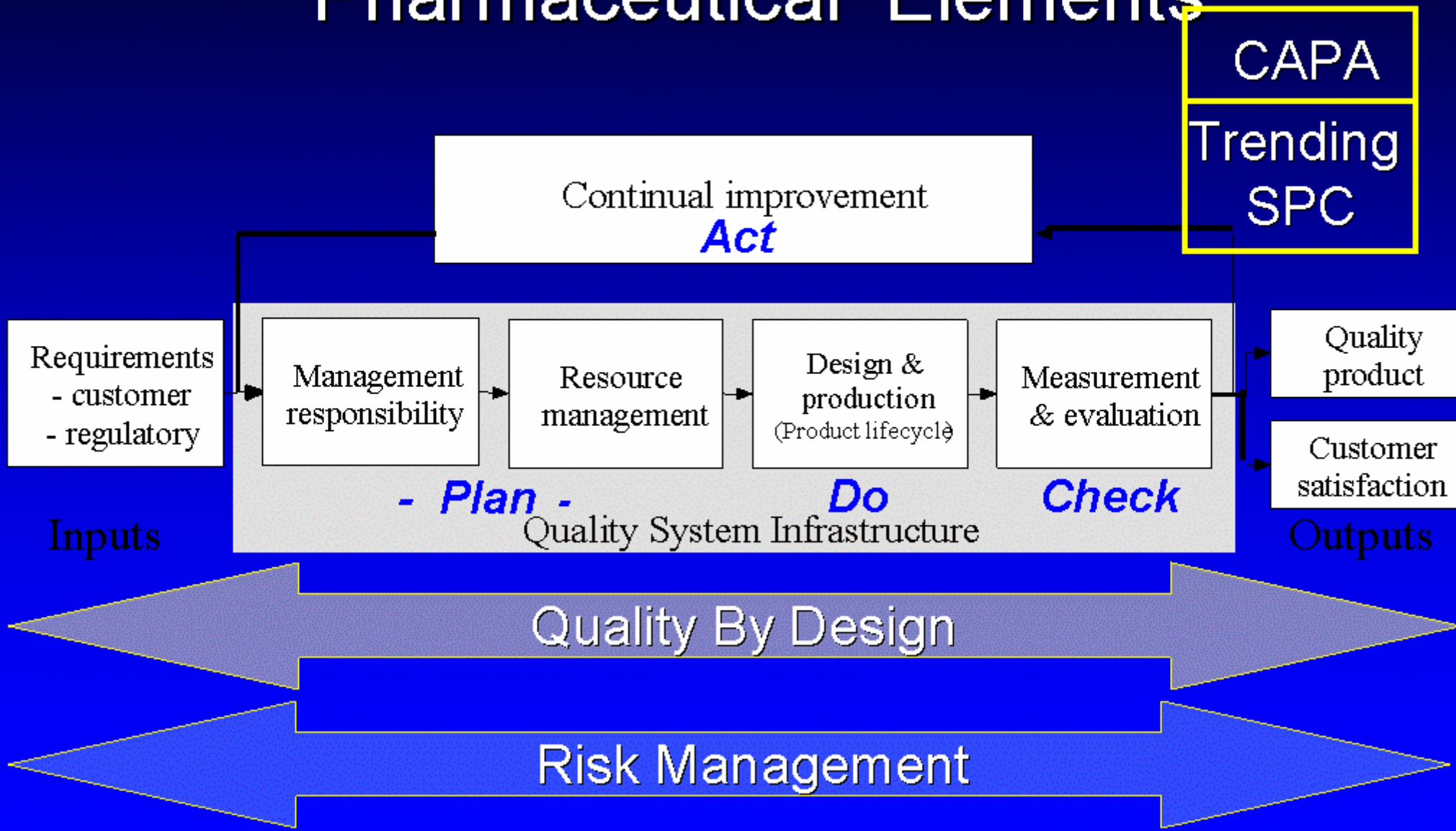
- CGMPs do not consider all elements of a modern, QS
- Different emphasis in CGMPs for pharmaceutical manufacture (than on some elements of a QS)
- Guidance describes a comprehensive quality system model and how CGMP regulations correlate to QS elements

Comparison of Quality Systems

- Numerous similarities between CGMP and modern Quality Systems as illustrated by guidance

- *"Quality should be built into the product and testing alone cannot be relied on to ensure product quality"*

Overview of A Modern Quality System w/ Pharmaceutical Elements



Differences Between Quality Systems and CGMPS

- Quality System provides greater emphasis than CGMP on some elements, for example
  - Quality management
  - Quality assurance
  - Risk Management
    - Evaluation analysis and quality risk management tools
  - Preventive action
  - Promote product and process improvement (i.e., continual improvement)
  - “Continual Improvement” of the Quality System

Differences Between Quality Systems and CGMPS

- CGMP provides greater emphasis than QS on some elements, for example:
- Processing equipment as much as testing equipment
- Higher standard for equipment calibration and maintenance
- Packaging and labeling controls
- Change control - more detailed consideration for adequacy of design and design of process controls

ICH Quality Systems (Q10)

(under development)

- Augments existing GMPs with quality system elements – bridge between regional regulations
- Applicable to drug substance and drug product for ”large and small molecules” throughout product lifecycle
- Describes an approach to developing an effective quality system
- Complements and facilitates Q8 and Q9
- Aimed at facilitating continual improvement

ICH Quality Systems (Q10)

(under development)

- Aligned with ISO Quality Management Systems, but in pharmaceutical application context
- Shift from CGMP compliance to comprehensive systems quality approach throughout lifecycle
- Key Elements
  - Quality System
  - Management Responsibility
  - Continual Improvement
    - Quality system
    - Product quality

Benefits of Implementing an Effective Quality System

- Inherent Benefits
  - Stronger role for Quality in Organization
  - Win:Win:Win – Patient, Industry, Regulator
    - Better tech transfer
    - Better process control and monitoring
    - Better change control
    - Improved process capability
    - Fewer non conformities, better investigations
    - Proactive approach
- To some extent, this will be dependent upon the acquired process and product knowledge (Q8), process validation information and use of Risk Management (Q9)

Benefits of Implementing An Effective Quality System

- Inherent Benefits can lead to Regulatory Benefits
  - Greater Efficiency in Review & Inspection
  - Better Regulatory Compliance
- Additional Potential Regulatory Flexibility
  - Impact on
    - CMC Review
    - Change control and continual improvement – Design Space
    - Submission of post approval changes
    - Inspection
    - Other potential regulatory benefits?

Challenges to Implementation

- Even with effective Quality Systems, other factors to consider in evaluating regulatory approach to potential benefits

Risk-based Regulatory Oversight

- Risk Assessment - The capability of process control strategies to prevent or mitigate risk
- The understanding of how manufacturing process factors affect product quality and performance – ability to predict impact of change with reasonable certainty
- Type of Product - complexity, intended use, manufacturing complexity
- Manufacturing operations critical to safety of product
- Products that serve a critical medical need, critical public health impact
- Compliance history, compliance status

Challenges in Implementation

- What is optional vs. what is required?
- How to evaluate a Quality System?
  - What is a correct metric?
- How to apply these to specific situations?
- How to apply QS to existing products?
- Greater integration of FDA review and inspection

The Future of Quality Systems

- General Approach – increase the level of Quality across all manufacturers
  - Reflective of modern quality systems elements
  - Strengthen role and importance of Quality Systems
- "FDA Quality Systems Approach" Guidance
  - No to replace any part of the CGMPs
  - Not to create any new requirements
  - Not to serve as an guide for FDA inspections
  - Reviewing docket comments and revising
- Participation in development of ICH Q10

The Future of Quality Systems

- Continuing evaluation of FDA CGMP (210 & 211)
  - Incremental approach to any changes in regulations
  - Intention to issue selective, targeted changes to regulations following standard rulemaking procedure
  - Possible changes to “quality regulations”
- Implementation
  - Based upon final changes in 210 & 211 regulations,
  - Possible revision to: Quality guidance, inspection programs, training programs, submission guidance, etc.

Considerations for Effective Quality Systems - So What's New?

- Why consistently cited GMP issues often related to role of Quality?
- Inadequate Quality Systems
  - Ineffective fundamentals (e.g., procedures)
  - Training & Experience
    - Appropriate training for Quality staff - knowledge and experience
  - Absence of Quality Culture/ Management Support?
  - Not integrated into organization as a partner
- Caution against "Quality for Quality Sake"
  - Form over function exercises
  - Excessive and unreasonable
  - Reasonable and effective application

Comprehensive and Consistent Implementation of GMPs through Effective Quality Systems

Implementation of Quality Systems at FDA

- SMG 2020 provides Quality System approach to internal FDA activities
- Review
  - CMC review Quality System
- Inspection
  - Team Bio, Pharmaceutical Inspectorate